International Standard Serial Number (ISSN): 2249-6807

International Journal of Institutional Pharmacy and Life Sciences 7(2): March-April 2017

INTERNATIONAL JOURNAL OF INSTITUTIONAL PHARMACY AND LIFE SCIENCES

Pharmaceutical Sciences

Research Article……!!!

Received: 30-01-2017; Revised: 29-03-2017; Accepted: 31-03-2017

SYNTHESIS AND ANTIBACTERIAL ACTIVITY OF NOVEL NAPHTHOFURAN DERIVATIVES

Jyot P. Vakharia[a], Vijay D. Gangan*[b], Aditya Giri[b], Ruchi S. Dubey[b], Jagdev S. Pujari[c], Amol P. Kharche[d], Maruti S. Satpute[d], Rajkumar Yadav[b] and Chaitaly T. Chakraborty[b]

a. Departmant of Chemistry, Bhawan's College, Andheri (West), Mumbai 400058.

b. Department of Chemistry, Thakur College of Science & Commerce, Thakur Village, Kandivali (E), Mumbai 400101.

c. Department of Chemistry, Shivajirao's Jondhale College of Engineering, Dombivali (East).

d. Department of Chemistry, R. D. National College and W. A. Science College, Linking Road, Bandra (W), Mumbai 400050.

Keywords:

Naphthofuran, Gram + ve and Gram – ve, Antimicrobial, Cascade approach, ^{1}H NMR, TOF MS ES, IR, Elemental analysis

For Correspondence:

Dr. Vijay D. Gangan

Department of Chemistry, Thakur College of Science & Commerce, Thakur Village, Kandivali (E), Mumbai 400101

ABSTRACT

Heterocyclic synthesis has emerged as powerful technique for generating new molecules useful for drug discovery. Heterocyclic compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs. A number of different synthetic approaches have been applied to synthesize naphthofuran moieties. We have attempted to synthesize various naphthofurans using a cascade reaction route. Three novel derivatives of naphthofuran were synthesized, characterized and tested for their potential antibacterial activity.

INTRODUCTION:

Heterocyclic synthesis has emerged as powerful technique for generating new molecules useful for drug discovery[1]. Heterocyclic compounds provide scaffolds on which pharmacophores can arrange to yield potent and selective drugs[2].Naphthofurans, in particular, possess a broad range of biological activities that are constituents of important natural products[3-5]. These plant extracts are being used for traditional medicines[6-9], and some of them for example mansonone D[10], Dunnione[11]*etc.* are also vital biologically active agents. Naphthofurans fused or coupled with nitrogen heterocycles do not occur in nature. A number of different synthetic approaches have been applied to synthesize naphthofuran moieties[12-16]. An interesting work on the synthesis of the naphthofuran moiety has been done by Wang *et. al*. They have used the approach of cascade reactions to synthesize naphthofurans.

Cascade reactions have emerged as a powerful tool to create complex molecular structures from simple starting materials. Cascade reaction approach, unlike the traditional step-wise bond formation approach, enhances greatly the synthetic efficiency, while generating less waste and minimizing the problems of handling chemicals.

We used different benzaldehydes for the reaction to synthesize different naphthofurans for the study of their antibacterial activity. We also changed the catalyst for the reaction, *viz*. triethylamine and carried out the reaction to study the effect of the catalyst on the cascade reaction.

MATERIALS AND METHODS:

Materials : Chemicals used were of a laboratory grade. The reactions were monitored by TLC on aluminium-backed silica plate visualized by UV-light.

Methods**:**General Procedure for synthesizing compounds (1) to (3) were summarized below.

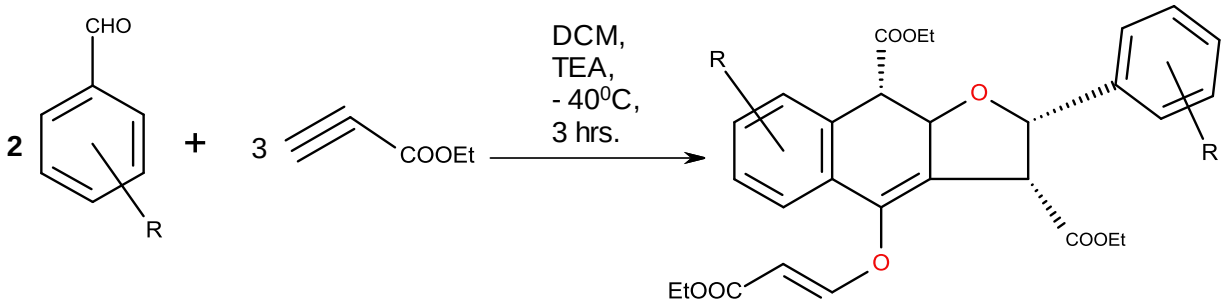
To a solution of benzaldehyde (2 mmol), and ethyl propionate (3 mmol) in dichloromethane (10 ml) was added drop wise a solution of (1.5 mmol) triethylamine (TEA) in 5 ml dichloromethane under nitrogen atomosphere at -40°C. The reaction mixture was stirred for 2-8 hours and constantly monitored by TLC using a solution of 10% ethyl acetate in hexane. The reaction mass was then quenched with 1.5 ml of 1N HCl solution at -40°C and then brought to the room temperature.

Workup:

The solution was washed with brine and dried over anhydrous sodium sulphate and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel with increase in concentration of ethyl acetate in petroleum ether to afford a pure product.

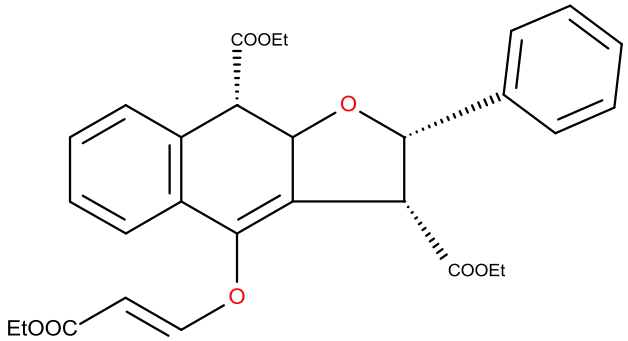
RESULTS AND DISCUSSION:

Reaction Scheme :



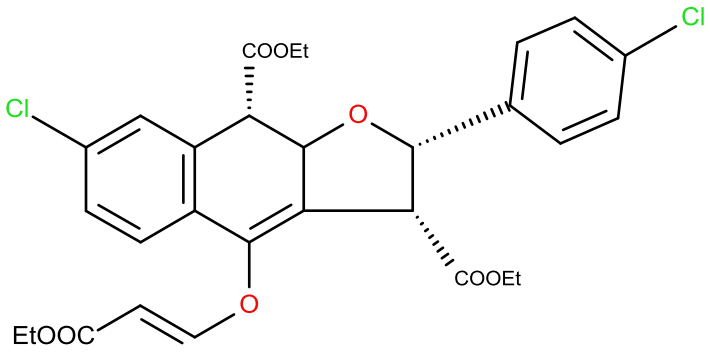
Using the cascade reaction shown above,we were able to synthesize and characterize the following different naphthofurans using their corresponding benzaldehydes along with ethyl propiolate.

Example 1 :diethyl (2S,3R,9S)-4-[(E)-3-ethoxy-3-oxo-prop-1-enoxy]-2-phenyl-2,3,9,9a tetrahydrobenzo[f]benzofuran-3,9-dicarboxylate



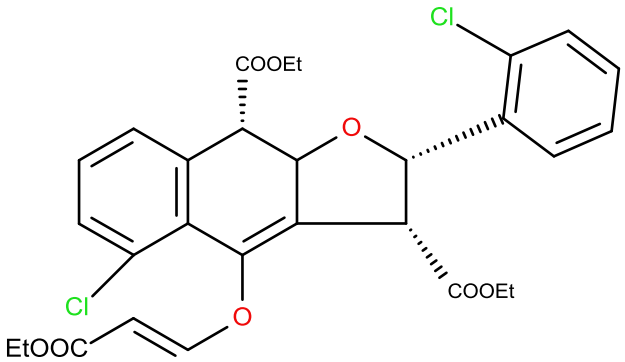
Off white solid: Molecular Formula $C_{29}H_{30}O_8$; Melting Range 128 – 130^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$)δ_{ppm} :-0.83 (t, *J* = 7.1 Hz, 3H), 1.22 (t, *J* = 7.1 Hz, 3H), 1.3 (t, *J* = 7.1 Hz, 3H), 3.71 (m, 2H), 4.04 (m, 2H), 4.12 (m, 2H), 4.39 (m, 2H), 5.44 (d, *J* = 12.4 Hz, 1H), 5.57 (d, *J*= 6.2 Hz, 1H), 5.78 (dd, J_1 = 1.2, J_2 = 13.3 Hz, 1H), 7.13 (m, 1H), 7.28 (m, 6H), 7.36 (d, *J*= 7.3 Hz, 2H), 7.60 (d, *J* = 12.4 Hz, 1H);^{13}C NMR (100 MHz, $CDCl_3$)δ_{ppm} :- 13.8, 14.48, 14.54, 52.1, 52.6, 60.4, 61.3, 61.7, 80.9, 85.1, 101.6, 123.1, 125.1, 126.4, 126.9, 128.3, 128.4, 129.3, 129.7, 131.9, 137.4, 142.4, 159.5, 166.8, 168.8, 172.3 ; IR(KBr) cm $^{-1}$:- 2981, 2938, 1739, 1719, 1642, 1452, 1373, 1321, 1275, 1189, 1119, 1035, 962, 747,702, 594; TOFMS ES : 529 (M + Na); Elemental Analysis, Requires C 68.76 % H 5.97 % O 25.27 % Found C 68.78 % H 5.99 % O 25.23 %.

Example 2 : diethyl (2S,3R,9S)-7-chloro-2-(4-chlorophenyl)-4-[(E)-3-ethoxy-3-oxo-prop-1-enoxy]-2,3,9,9a-tetrahydrobenzo[f]benzofuran-3,9-dicarboxylate



Pale yellow solid; Molecular Formula $C_{29}H_{28}C_{l2}O_8$; Melting Range 136 – 138^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$)δ_{ppm} :-0.87 (t, *J* = 7.1 Hz, 3H), 1.25 (t, *J* = 7.1 Hz, 3H), 1.33 (t, *J* = 7.1 Hz, 3H), 3.74 (m, 2H), 4.07 (m, 2H), 4.15 (m, 2H), 4.42 (m, 2H), 5.48 (d, *J* = 12.4 Hz, 1H), 5.60 (d, *J* = 6.2 Hz, 1H), 5.80 (dd, J_1 = 1.2, J_2 = 13.3 Hz, 1H), 7.15 (m, 1H), 7.3- 7.8 (m, 4H, ArH), 7.36 (d, *J* =7.3 Hz, 2H), 7.60 (d, *J* = 12.4 Hz, 1H); TOFMS ES : 597 (M + Na); Elemental Analysis, Requires C 60.53 % H 4.90 % O 22.24 %Cl 12.32 % Found C 60.57 % H 4.94 % O 22.27 %.

Example 3 : diethyl (2S,3R,9S)-5-chloro-2-(2-chlorophenyl)-4-[(E)-3-ethoxy-3-oxo-prop-1-enoxy]-2,3,9,9a-tetrahydrobenzo[f]benzofuran-3,9-dicarboxylate



Off white solid: Molecular Formula $C_{29}H_{28}C_{l2}O_8$; Melting Range 140 – 142^{0}C; ^{1}H NMR (400 MHz, $CDCl_3$)δ_{ppm} :-0.90 (t, *J* = 7.1 Hz, 3H), 1.28 (t, *J* = 7.1 Hz, 3H), 1.35 (t, *J* = 7.1 Hz, 3H), 3.74 (m, 2H), 4.10 (m, 2H), 4.16 (m, 2H), 4.45 (m, 2H), 5.50 (d, *J* = 12.4 Hz, 1H), 5.62 (d, *J* = 6.2 Hz, 1H), 5.82 (dd, J_1 = 1.2, J_2 = 13.3 Hz, 1H), 7.22 (m, 1H), 7.2 - 7.7 (m, 4H, ArH), 7.40 (d, *J* = 7.3 Hz, 2H), 7.60 (d, *J* = 12.4 Hz, 1H); TOFMS ES : 597 (M + Na); Elemental Analysis, Requires C 60.53 % H 4.90 % O 22.24 % Cl 12.32 % Found C 60.56 % H 4.94 % O 22.28 %.

We attempted the synthesis of the naphthofurans moieties using the following benzaldehydes and catalysts.

Name of Benzaldehyde	Time of Reaction	Catalyst Used	Yield
(1) Benzyaldehyde	3h	Triethylamine	32%
(2) 2-Chloro benzaldehyde	2h	Triethylamine	21%
(3) 4-Chloro benzaldehyde	2h	Triethylamine	27%

As seen from the above table, we also tried changing the catalyst for the reaction from Triethylamine to diethylamine, aniline and di-isopropylethylamine. We found that the reaction did not proceed in case of diethylamine and aniline. Thus we could conclude that the reaction only proceeds in the presence of a tertiary amine. Additionally, we also attempted the synthesis of thenaphthofurans using 4-hydroxy and 3-hydroxy benzaldehydes, but the reaction did not taken place. On the other hand, the chlorobenzaldehydes did give a product but in low yield and thus believe that the phenolic hydroxyl group on the benzaldehyde was unfavourable for the reaction.

EXPERIMENTAL :

Melting points were determined on a Thomas Hoover capillary melting point apparatus using digital thermometer. ^{1}H NMR spectra were recorded on a Varian 400 MHz spectrometer in $CDCl_3$. Chemical shifts were recorded in parts per million down field from tetramethylsilane. Mass spectra were recorded on a TOF MS ES mass spectrometer. Elemental analysis were carried out as a percentage on a Thermo finnigan, Flash EA 1112 series, Italy.

CHROMATOGRAPHIC SYSTEM :

Column chromatography : For column chromatography 100 – 200 mesh Acme grade silica gel is used. The crude reaction mixture is concentrated under reduced pressure to yield crude mass which is preadsorbed on silica gel and purified by column chromatography with increase in concentration of Ethyl acetate in Hexane. The fractions having similar 'R_f" values were pooled together,concentrated and subjected for characterization using various spectroscopic techniques.

Thin layer chromatography : TLC plates were prepared using silica gel G (ACME, BOMBAY). Hexane :EtOAc (90 : 10) was used as the solvent system.

Radial chromatography : The circular glass plates of thickness 1 mm, were prepared by using silica gel (PF254, E. MERCK, 50 g) in cold distilled water (105 ml). For elution, gradually increasing concentrations of EtOAc in pet ether were employed.

BIOLOGICAL ACTIVITY :

Antibacterial Activity using ditch plate method[17] :-

The synthesized molecules were screened for their antibacterial activity at 100 µg/ml concentration using ditch platemethod against Gram positive (*Staphylococcus aureus,*

Corynebacteriumdiphtheriae) and Gram negative (*Escherichia coli, Klebsiella pneumonia, Salmonella typhi)* bacterial species qualitatively. The results of the antibacterial activities are summarized in Table 1.

Theory: Ditch plate method is the method of chosen to test the anti-bacterial activity of compounds. It is a preliminary method to screen the anti-microbial potential of compounds / drugs, which are insoluble or partially soluble in aqueous phase. In this method, the test compound is seeded in an agar plate and the test organisms are streaked across to test the inhibition of the growth as a marker of anti-microbial activity.

PROCEDURE: A ditch (10mm x 70mm) is cut into sterile MH agar plate. The test drug / compound is added to 5 ml molten MH agar butt at 40^0C and this mixture is poured into the ditch and allowed to solidify. The ditch should be made in level with the rest of the agar by pouring the mixture . The different bacterial cultures are streaked perpendicular to the ditch using nichrome wire loop. The plate is then incubated at 37^0 C for 24 hours.The results are observed as inhibition of bacterial growth on the ditch as well as adjacent to the ditch.

Table 1: Antibacterial Activity Results

SAMPLE NO.	ACTIVE AGAINST
1	*Corynebacteriumdiphtheriae* [Gram positive] *Klebsiellapneumoniae* [Gram negative]
2	*Staphylococcus aureus*[Gram positive] *Salmonella typhi*[Gram negative] *Klebsiellapneumoniae* [Gram negative] *Corynebacteriumdiphtheriae* [Gram positive] *Escherichia coli* [Gram negative]
3	*Staphylococcus aureus*[Gram positive] *Salmonella typhi*[Gram negative] *Klebsiellapneumoniae* [Gram negative] *Corynebacteriumdiphtheriae* [Gram positive] *Escherichia coli* [Gram negative]

The above results shows that the molecules (1), (2) and (3) has antibacterial activity against both the bacterial cultures. Thus, simple aryl (1) and especially halo aryl (Compound 2 and 3) werepotential antibacterial candidates.

CONCLUSION: The three novel derivatives of naphthafuranwere synthesized using Cascade approach possessing potential Antibacterial activity. In depth analysis of these compounds

through structure activity relationship studies would provide further insight and can be an interesting topic of future studies. The structural diversity and the pronounced biological activities encountered in the naphthofuranderivatives suggests that this class of compounds is worthy for further studies that may lead to derivatives by using combinatorial chemistry approach is an alternative strategy to new therapeutic discovery. In other words the generation of diverse naphthofuranderivatives develop new therapeutic molecules that might result in candidates having better activity.

REFERENCES:

1. Hermakens P. H., Ottenheijm H. C., Rees D. C. Solid phase organic reactions II. A review of literature. *Tetrahedron*, 1997, 53, 5643 – 5649.
2. Gordon E., Barrett R. W., Dower W. J., Foder S. P. Applications of combinatorial technologies to drug discovery. II. Combinatorial organic synthesis, library screening strategies and future directions. *J Med Chem.*1994, 37, pp. 1485 – 1490.
3. Price J. R.; Robinson, R. The yellow pigment of Papavernudicaule. Part II'. *J. Chem. Soc.*,1940, 1493 – 1499.
4. Stochigt J.,Srocka U., Zenk M. H.Stucture and Biosynthesis of a new Anthraquinone from Streptocarpusdunnii. *Phytochemistry* 1973, 12, 2389 – 2391.
5. Inoue K., Ueda S., Nayeshiro H.,Inouyet, H. Quinones of streptocarpusdunnii. *Phytochemistry*,1983, 22 (3), 737-741.
6. Ruedi P., Eugaster C. H. Helv.Isolierung von (−)-Dunnionaus*Calceolaria integrifolia* MURR. *(Scrophulariaceae.) Chem. Acta.*,1977, 60, 945 – 947.
7. Yoshinori F., Tadashi E., Chikako M., Yuji O., Katsumi K., Hidetsugu T., Masayoshi A., Kazuhiko I., Keiji Y., Nobuo I., Osamu Y. and Tetsuro I.; Studies on the structure and stereochemistry of cytotoxic furanonaphthoquinones from Tabebuiaimpetiginosa: 5- and 8-hydroxy-2-(1-hydroxyethyl)naphtho[2,3-b]furan-4,9-diones**.***J. Chem. Soc., Perkin Trans. 1*, 1991, 2323-2328.
8. Rohatgi B. K., Gupta R. B., Roy D. and Khanna R. N.;Quinones from tecomapentaphylla : constitution of tecomaquinones. *Indian Journal of Chemistry*,1983, 22B, 886- 890.
9. Khanna R. N., Sharma P. K. and Thomson R. H.;A revised structure for dehydrotectol and tecomaquinone. *J. Chem. Soc. Perkin Trans.1*, 1987, 1821 - 1824.
10. Bettolo G. M. B., Cassinovi C. G. and Galleffi C.;A new class of quinines :sesquiterpenoid quinines of Mansoniachev. *Tetrahedron. Lett.*,1965, 4857 – 4864.
11. Price J. R. and Robinson R. J.; *J. Chem. Soc.*,1939, 1522 – 1529.

12. Wang Y. G., Cui S. L.and Lin X. F.;A Highly Selective Cascade Approach to Diverse Aromatic Ring Systems from Simple Aromatic Aldehydes and Propiolates. *Org. Lett.*, 2006, 8(6), 1241-1244.
13. Nagaraja K. G., Kumarswamy M. N., Vaidya V. P. and Mahadevan K. M.;Microwave assisted synthesis of naphtha[2, 1-b]furan-1,3,4-benzotriazepines : a potent antimicrobial agent. *ARKIVOC*, 2006, 211-219.
14. Mahadevan K. M.,Basavaraj P. and Vaidya, V. P.;Studies in Naphthafurans : Part V-synthesis of 2-aryl-1,2,3,4-tetrahydropyrido(naphtha[2,1-b]furan)-4-ones and their biological activities. *Indian J. Heterocyclic Chem.*,2001, 11, 15 - 18.
15. Latha K. P., Vaidya V. P., Keshavayya J. and Vijaya Kumar M. L.;Synthesis, characterization and biological studies of metal complexes of 2-acetylnaphtho[2,1-b]furan. *Nat. Acad. of Sci. Letter*, 2002, 25(5-6), 153 - 158.
16. Kumaraswamy M. N. and Vaidya, V. P.;Novel method for the synthesis of symmetrical and asymmetrical azines involving naphtho[2,1-*b*]furan and their antimicrobial activity. *Indian J. Heterocyclic Chem.*, 2005, 14, 193 - 198.
17. Finn R. K.; Theory of Agar Diffussion Methods for Bioassay. *Anal. Chem.*, 1959, 31 (6), pp 975 – 977. b) Al lafi T *et. al.*; The effect of miswak used in Jordan and Middle East on oral bacteria. *International Dental Journal*, 1995, 45 (3), pp. 218 – 222.